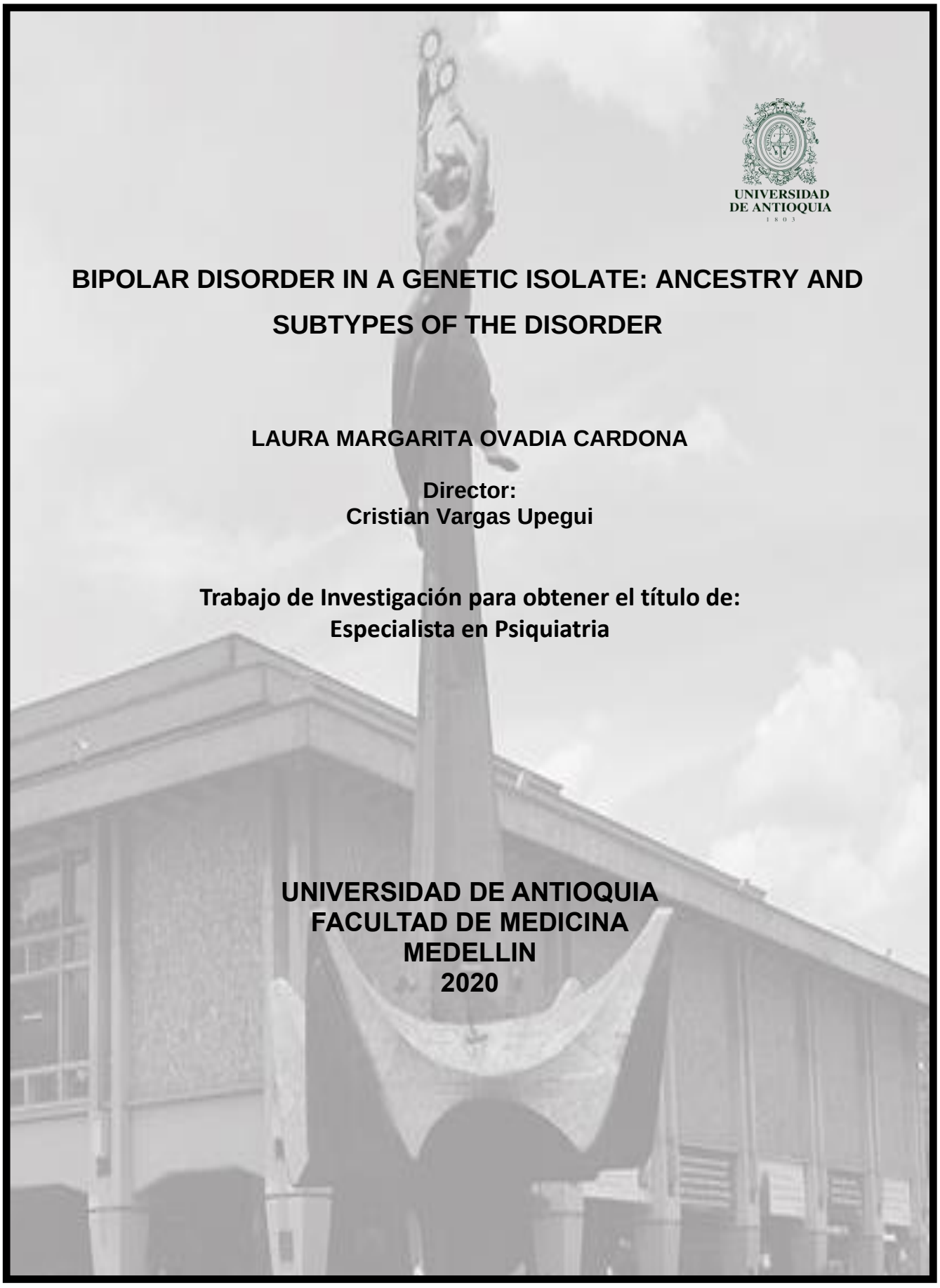

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BIPOLAR DISORDER IN A GENETIC ISOLATE: ANCESTRY AND SUBTYPES OF THE DISORDER

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Abstract

Background: While broad, the current diagnostic category of Bipolar Disorder (BD) may not cover or describe the full clinical spectrum of this clinical condition. One potentially important factor lacking in previous research is the exact ancestral composition of the clinical samples.

Objective: To define subtypes of BD in a genetic isolate (paisa population) using sociodemographic, clinical and ancestral composition variables, in efforts to generate various conglomerates that might be useful for determining the natural history of BD.

Methods: We performed a cross-sectional study on a clinical sample of 164 patients diagnosed as Bipolar I or Bipolar II disorder as defined by DSM-IV-TR. Latent Classes Analyses were used to examine the interaction of the ethnic composition of the sample, rigorously defined using specific genetic markers, with clinical variables (number of previous episodes) and the therapeutic response to treatment with lithium.

Results: the best fitting model resulting from the analyses consisted of six latent classes (LC) including ancestry composition, number of depressive and manic episodes, and clinical response to lithium treatment: LC-1 consisted of patients with predominantly European ancestry, having a small number of clinical episodes of mania/depression, and showing a good response to lithium; LC-2 consisted of patients with predominant Amerindian ancestry, presenting few clinical episodes, and showing an intermediate response to lithium; LC-3 consisted of patients with predominant African ancestry, intermediate number of clinical episodes, and showing a poor response to lithium. LC-4 grouped patients with predominant Amerindian ancestry, with an intermediate number of clinical episodes, and showing a partial response to lithium; LC- 5 consisted of patients with predominant Amerindian ancestry, multiple clinical episodes, and showing a poor response to lithium; LC-6 consisted of patients with predominant European ancestry, multiple clinical episodes, and showing the best response to lithium.

Conclusion: On the basis of these results, we propose six latent subtypes of BD. We show that a rigorously defined ancestry component significantly influences clinical and treatment outcomes. This latent classification may be useful in describing the genesis, course and evolution of this heterogeneous disorder and may lead to a more personalized management of individual cases.

Keywords: Bipolar Disorder, Subtypes, Latent Classes, Ancestral Composition, Ethnic Composition, Genetic Markers

INTRODUCTION

Bipolar Affective disorder (BD) is a serious mental disorder characterized by recurrent episodes of mania, hypomania, or depression. Its prevalence worldwide ranges from 3% to 7% (1), and it is much higher for subclinical forms (2). BD affects a person's functions and quality of life, imposes a high burden on the health and public assistance systems (3,4), and strongly impacts unemployment rates (5,6). Complications such as suicide are frequent (2). Because of all these issues, an early and accurate clinical diagnosis and implementation of appropriate treatment are of vital importance.

Even though the classic signs and symptoms of BD are quite distinct, particularly in the case of manic episodes, there are complex and polymorphic variations in the clinical presentation of the syndrome. For example, psychotic symptoms may be the predominant clinical presentation in up to 53% of cases (7) and comorbidity with other mental disorders such as anxiety and substance use disorder can modify the clinical presentation and course of the disorder (8,9)**.**

The origins of the BD classification in modern psychiatry were established by Emil Kraepelin In the 19th century, who defined "manic-depressive insanity" as a disorder of the regulation of a person's arousal, activity, and mood, presenting various symptoms and levels of functional severity (10). The term 'bipolar' was first used by Leonhard in 1957 to refer to disorders that included depressive and manic episodes (11). The distinction between BD-I and BD-II came later with Fieve and Dunner (12), who associated BD-I to the presence of florid manic episodes (episodes of great excitement or euphoria, delusions and overactivity that require hospitalization) and BD II to the less severe elevations of mood technically labeled as

hypomania. This conceptualization was maintained in the classification systems of the American Psychiatric Association (DSM) and the World Health Organization (ICD). However, using this discrete approach, several intermediate or incomplete forms of BD cannot be properly designated or classified. This has led some authors to use the term “bipolar spectrum” as an overarching model to encompass the different manifestations of BD, placing the classic episodes of mania and depression on opposite sides of the spectrum and a number of subthreshold symptoms in between (13,14).

A key element for allocating patients into the BD-I and BD-II categories is the severity of the clinical manifestations, with a tacit acknowledgment that BD-II is less severe than BD-I. However, subthreshold symptoms have been reported to generate severe dysfunction (15) and the suicide risk appears to be comparable in BD-I and BD-II, with an annual average prevalence of suicide attempts of 25.6% and 20.8% respectively (2). Moreover, other unfavorable clinical characteristics have been reported in patients with BD-II, such as presenting a greater number of affective episodes, depressive recurrences, and significant comorbidity with anxiety (16). This suggests the existence of extensive phenomenological variability that cannot be explained by the official subtypes (17).

If only clinical variables are taken into account, the limits for the diagnosis may remain blurry, not fully explaining or clarifying the limited validity of the current diagnostic categories. For this reason, several experts have recommended a refinement of the diagnostic approach through the use of laboratory, family history, and treatment adherence data, so that more homogeneous subgroups can be described which should enhance the diagnostic validity (18). Likewise, the characteristics of the clinical course or response to treatment of various patient subgroups can

provide relevant information for clinical practitioners, thus allowing us to identify which patients or subgroups may require specific interventions or support (19).

One of the characteristics that may impact the clinical course and treatment response is ethnic origin. Latino bipolar patients in the United States have been found to present more depressive symptoms, while African-Americans tend to show an earlier onset, more psychotic symptoms, and a greater functional compromise than members of the general population (20–22). Likewise, it has been suggested that there are ethnic differences in the response to lithium (23). Most of the above research has been done in North America and therefore, an assessment of Latino-origin populations outside the United States seems in order. For this reason, we decided to evaluate patients in the “paisa”, region of Colombia. The “paisa” are a genetic isolate inhabiting the Andean region of Colombia whose ethnic origin resulted from an admixture of Amerindian maternal lineages with European paternal lineages and, to a lesser extent, African admixture (24,25). With large genealogies, geographic grouping and sharing sociocultural characteristics, this isolate represents a population that allows hereditary traits to be evaluated in depth and variance from the environment to be reduced (26). The identification of subtypes in this group may lead to a better understanding of the underlying mechanisms of BD and allow more personalized clinical and therapeutic approaches in this population. Our group has been actively engaged in clinical and genetic research focusing on this population for more than two decades (24–27).

In this study we theorize that there are several clinical subtypes, in addition to BD-I and BD-II, that make up the full spectrum of BD. Our overarching aim is to search for possible BD latent subtypes that incorporate an assortment of sociodemographic, ancestral and treatment

response variables. We posit that this strategy can improve the clinical knowledge and understanding of the natural history of BD and that it may lead to more precise clinical management. This strategy may be useful for selecting more homogeneous cohorts for research purposes and follow up studies.

METHODS

This is a descriptive, cross-sectional study, carried out by the Research Group on Psychiatric Disorders (GIPSI) of the University of Antioquia, in Medellin, Colombia. The project was approved by the Bioethics Committee of the School of Medicine of the University of Antioquia and abides by the principles that protect the rights of the participants according to the Resolution No. 008430 of 1993 of the Ministry of Health, Republic of Colombia, and the Declaration of Helsinki. Informed consent was obtained from all participants.

Participants: Adults older than 18 years, with diagnosis of BD-I and BD-II, seen at the outpatient clinical facilities of the *Hospital Universitario San Vicente Fundación* in the city of Medellín and at the *Clínica San Juan de Dios* in Manizales, both located in the midst of the "paisa" region of Colombia, were recruited. To enter the study, patients needed to fulfill DSM-IV-TR criteria for bipolar disorder. Patients entering the study should have been on lithium treatment for at least six months according to the patient's report and medical history. Those patients with a history of any neurological disorder, intellectual disability, or medical disorders whose manifestations might overlap those of BD, were excluded**.**

Instruments and Clinical Procedures:

DIGS: DSM diagnoses were derived from clinical face to face interviews using the diagnostic interview for genetic studies (DIGS) version 3.0, which was validated specifically for this

Spanish-speaking population by our research group (28). The DIGS elicits all relevant clinical and sociodemographic variables for diagnosing major mental disorders e.g., mood, psychotic, anxiety and substance use disorders.

Lithium Response: To evaluate the response to lithium, the ALDA scale was used. This instrument has two parts: Part A evaluates how the course of the disease has changed under lithium treatment. Part B helps to establish whether or not there is a causal relationship between clinical improvement and treatment with lithium. The total score in the ALDA scale (TS) is obtained by computing the results from both Part A and Part B.. (29). For these analyses, we used three possible categories of treatment response: Poor Response (PR) = total score (TS) less than 2; Partial Response (PR), TS between 2 and 6; Good Response (GR), TS equal or greater to 7. The ALDA scale was administered by research assistants, all with clinical training (recently graduated physicians or psychology PhD students). These assessments were done either in person or by telephone in the case of patients who could not come to the clinic.

Founder Effect and Genetic Isolation of “Paisa” Community: To designate a patient as “paisa” we used the isonymy strategy. This is the study of the frequency and distribution of last names in human populations. According to recent reviews, as many as 195 specific last names are characteristic of “paisa” populations. This is inferred from such sources as the list of last names among first settlers, population census of the region, birth certificates from parish books, and a systematic review of traditional and current last names commonly found in the region. In these reviews, the predominance of Amerindian, European and African ancestry was also noted (30).

In terms of previous episodes, patients were allocated into three possible groups: those with less than two episodes (***few***), those with 2-7 episodes (***intermediate)*** and those with 8 or more episodes (***many)***.

All clinical evaluations were done face to face by trained psychiatrists.

DNA Extraction and Genotyping of Ancestry Markers: DNA extraction was performed with phenol-chloroform. Ten ancestry informative markers (AIMs) were genotyped using polymerase chain reaction (PCR) by conventional methods. AIMs were selected if the delta values were equal to or greater than 0.6 (chosen from HAPMAP, the Affimetrix® database and dbSNP), which allows to discriminate the ancestral structure of the sample as European, American, Indian, and African; The enzymatic digestion products of the amplicons were separated by electrophoresis on agarose gels (2 to 4%) and visualization was done with ethidium bromide (EtBr).

The estimations of the average and individual ancestral admixture, and the degree of population structuring, were obtained with the methods implemented in the ADMIXMAP software (31). This allows for defining the admixture ratio of each gamete in the sample, under the assumption of the Hardy-Weinberg equilibrium. Additionally, the proportions estimated with ADMIXMAP were compared with those estimated with the methods implemented in the STRUCTURE V2.2 program (32), which uses a Bayesian model, very similar to that used by ADMIXMAP, with the difference that STRUCTURE V2.2 assumes no independence of the gene frequencies and therefore allelic correlations are allowed in subpopulations. A model of

K = 3 (parental populations) and 50,000 repetitions was used in which K1 was the Amerindian, K2 the African American and K3 the European population. This clustering method uses genotypic data to determine the presence of population structure, with the assignment of individuals to populations, and the identification of migrant and/or mestizo individuals. With these parameters, estimates of the diversity of the population, within and between them, were obtained using the methods implemented in Arlequin version 3.1 (33).

Statistical analysis: An Excel database was created and reviewed by two evaluators to verify the quality of the data. The characteristics of the sample were summarized using descriptive statistics. Frequencies and percentages were calculated for the qualitative variables, and the median and interquartile range were estimated for the quantitative variables (normal distribution adjustment was evaluated by the Kolmogorov-Smirnov test). Data processing and information analyses were done with STATA® Version 15.

Classification techniques are generally used to define subtypes within heterogeneous samples by grouping associated/correlated variables without suggesting causal relationships on a dependent variable. As there are no criteria to determine the optimal number of subgroups, we used latent class analysis (LCA), a strategy that is increasingly being used in psychiatry and other medical disciplines. The LCA is a categorical analog of the factor analysis and its basic premise is that a heterogeneous group can be partitioned into several homogeneous subgroups whose underlying relationship structure is explained by one or more unobserved (or latent) variables. This allows researchers to evaluate the existence of groups showing similar patterns/profiles (34). The clinical and sociodemographic variables were taken as ‘indicator’ variables (age of onset of the disease, number of manic and depressive episodes, total number

of episodes, predominant polarity, history of psychosis, suicidal behavior, number of hospitalizations and comorbidity with other mental disorders, including substance use disorder).

An expectation-maximization algorithm was used with the LATENT GOLD 4.0® program (Statistical Innovations, Belmont, MA). Models that estimated solutions from 1 to 10 classes were compared. To define the model fitting the best, the goodness of fit statistics were used as criteria with the LATENT GOLD 4.0® integrated log algorithm (Log-Likelihood -LL-) and the change in the Bayesian Information Criterion (BIC for its acronym in English). The fit was found to improve by decreasing LL and BIC. The estimated probability of each indicator variable was plotted according to class, ensuring a rescaling between 0 and 1. The variables included in the final model were those that reached statistical significance with an alpha level of 5%. The characteristics of each subtype were defined using descriptive statistics.

RESULTS

Of the 172 patients entering the study, 8 had to be excluded due to incomplete data. Therefore, a total of 164 participants were included in the analyses.

A majority of the sample were females, and the predominant polarity was manic. Comorbidity with another mental illness was greater than 30% and the average ALDA score was 3 points (**Table 1**).

Latent Class Analysis

According to the LL and BIC values, the best fitting model is the one depicting the existence of 6 main latent classes **(Table 2).** Relevant clinical, demographic, and ethnic characteristics are shown in **Table 3.** The key variables included in the LCA were ancestry (Amerindian, European, African), total number of affective episodes (including depressive and manic episodes) and scores in the ALDA scale **(Figure 1).** Based on these variables and their interactions, the following empirical subtypes (latent classes) can be defined:

Subtype 1: European Ancestry - Few episodes - Partial response to lithium

These are patients with predominance of European ancestry who display fewer manic (this being the predominant polarity), depressive, and total episodes. They presented a low number of hospitalizations in relation to other groups and exhibit a partial lithium response profile, being the second-best response group (25%).

Subtype 2: Amerindian Ancestry - Few episodes – Partial response to lithium

These are patients with predominance of Amerindian ethnicity. They have the least number of manic, depression, and total episodes, with the manic polarity being predominant. They presented the fewest hospitalizations of all groups and have an intermediate response to lithium.

Subtype 3: African Ancestry - Intermediate episodes – Partial response to lithium

These patients have predominant African ethnicity and are the third group with the highest number of affective episodes and although there is a significant percentage of patients with undetermined polarity, the manic polarity was predominant (56.7%). Even though they have a mean ALDA TS of two, corresponding to a partial response, this group exhibits poor response to lithium profile, with 40% not responding and only 3.3% having a good response. They also had the lowest percentage of men of all groups.

Subtype 4: Amerindian Ancestry - Intermediate episodes - Partial response to lithium

Patients with predominant Amerindian ethnicity have an intermediate profile of affective episodes, in which the manic polarity predominates. They also have the lowest prevalence of substance use disorder and an intermediate response to lithium; they are the older patients.

Subtype 5: Amerindian Ancestry - Many episodes - Poor response to lithium

These patients have an Amerindian ethnic predominance and have the highest number of affective episodes. In relation to this, they present the highest proportion of depressive polarity of all the groups. It is the second group with the lowest age of onset of BD. They also presented more hospitalizations, higher prevalence of BD-II, higher percentage of male patients and

higher comorbidity with substance use disorder. They have the worst response to lithium, with 50% of individuals showing no response.

Subtype 6: European Ancestry - Many episodes - Partial response to lithium

These patients have the highest prevalence of European ancestry. They presented a lower age of onset of BD and have a high prevalence of affective episodes, where the manic polarity is predominant over the depressive one. They also presented a high number of hospitalizations and were the group with the best response to lithium.

DISCUSSION

Through a latent class analysis, we propose here six empirical subtypes of BD each with differing assortments of ancestry, clinical features and treatment response. Of these six subtypes, the two groups with predominant European ancestry showed the best response to lithium but differed from each other by the number of episodes presented. One group with predominant African ancestry showed a poor response to lithium while the three groups with a predominant Amerindian ancestry showed differences in both the number of episodes and the response to lithium.

The two groups with predominant European ancestry showed a good response to lithium, suggesting a positive association between these variables but being independent of the number of episodes. This result is of clinical relevance due the limited information in the literature on the association between ancestry and response to lithium. If replicated, this could optimize the management of BD in this population since lithium is considered the first line pharmacological treatment for individuals with a predominance of European ancestry who have no contraindications for its use.

In the case of patients with a predominant African-American ancestry, response to lithium was poor and there was an intermediate number of affective episodes. These results differ from those of González et al (23) who reported that in the United States, African Americans showed a better response to lithium than whites. These authors measured improvement in functional capacity and scores in depression scales during a 6-month follow-up. However, ethnicity was simply defined by self-report, which falls short of a comprehensive characterization of individual ancestry (35,36). This shortcoming may have affected their results, leading to a biased

estimate of the impact of ancestry on the outcome of the study. Another study, also in the United States, reported more susceptibility to the adverse effects of lithium in African American patients, recommending the use of lower lithium doses in populations with significant African ancestral components (37) and recommending other therapeutic options for this group.

In our study, three subgroups with a predominant Amerindian ancestral component were found. One of these groups showed the highest number of affective episodes (primarily depressive episodes) in our full sample, and also poor lithium response, early onset of illness and a higher prevalence of comorbid substance use. These characteristics were present to a lesser extent in the other two groups of Amerindians who had fewer affective episodes and a better response to lithium, in addition to a predominant manic polarity.

Previous research reports support the association of manic polarity with a better response to lithium and depressive polarity with worse response and more relapses. Other factors that have been associated with poor response to lithium are early onset of the disease and comorbid substance use disorder (SUD)(38,39) . This is concordant with the characteristics present in the first BD subgroup we have proposed, with a high Amerindian ancestral component that was associated with greater clinical severity (16,40). According to the findings of our study, in individuals with high Amerindian ancestral component, the worst course is determined by a predominant depressive polarity, early onset of BD, and SUD.

To the best of our knowledge, few studies have included cluster analyses in their design with the aim of proposing or separating different subgroups under the bipolar umbrella. Bauer et al., (41) in a study of 4037 BD-I patients reported the existence of a few subgroups, placing a

primary focus on age of onset. These authors documented prominent family history of mental disorder and a salient first affective episode (depression) in the youngest subgroup. Bauer et al, also found that BD groups with the earliest age of onset had a higher number of affective episodes (41). Studies like this one can help allocating BD patients into more discrete subgroups and this may enhance clinical assessment, management, and follow up of these patients through offering a more personalized approach. This is also important for research purposes, as the description of inclusion criteria for patient recruitment into genetic association studies can become more precise, thus capturing the various historical, clinical and therapeutic elements that impact the genesis, development and course of this major psychiatric disorder. Likewise, this model can be also applied to clinical trials with the goal of assessing pharmacological response and enhancing the therapeutic efficacy, through reducing the heterogeneity of the original BD syndrome.

By establishing the existence of various subgroups with different assortments of ancestry, clinical characteristics and treatment response, our report should help understand various elements that add to the complexity of BD. While the literature has shown an association between clinical and sociodemographic variables and response to lithium, few studies have provided meaningful information about the relevance of the racial/ethnic (ancestry) component and lithium response. The findings in this study strongly suggest that ancestry influences the response to lithium, and point to the existence of unique pharmacogenetic or pharmacokinetic factors is some populations. In fact, a number of genetic variations related to lithium response have been previously described. These include single nucleotide polymorphisms (SNPs) harbored in genes encoding the brain-derived neurotrophic factor (BDNF), the neurotrophic receptor tyrosine kinase 2 (NTRK 2), pathway Cg1 phospholipase of inositol and the CREB

protein (42–44). It is well known that these polymorphisms have a differential allelic frequency distribution in several human populations, and therefore this could be one of the reasons for the variance of lithium response in populations. To further clarify this, it would be useful to study not only SNPs but also how their distribution in populations influence the response to this drug. Knowledge of the genetic profile of individuals could facilitate decision-making related to the management of mental disorders. Advances in pharmacogenetics and the description of more discrete subgroups would advance pharmacotherapy, providing guidance on choice of drugs, their doses and treatment schedules tailored to each group, a process now called “precision medicine”

Limitations:

Limitations of this study include a relatively small sample size, a fact that may limit the statistical significance of some comparisons (e.g., BD severity, presence of psychosis, suicidal behavior, and number of hospitalizations). Likewise, even though the clinical evaluation was carried out with a standardized interview, clinical data are subject to memory recollection and personal characteristics of the individuals reporting them, so there is a possibility of bias.

Conclusion

In the ‘Paisa’ genetic isolate, six latent subtypes of BD were identified each including an important ancestral component that appears to influence the clinical course of the disorder and the differential response to lithium. This proposed classification may be useful for allocating patients into discrete groups that may have practical and predictive value and may lead to a more personalized management of these patients.

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Author contributions

CDVU, MAB, CALJ concept and designed the study, LMOC, MAB and JPZO performed the statistical analysis. JPZO, LMOC, JMCA, MAB drafted the manuscript. All authors contributed in interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

Competing Declaration of Interest

The authors declare no conflict of interest.

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Tables.

Table 1. Clinical, sociodemographic and ancestry variables in subjects with BD from a "paisa" genetic isolate

Variable	Number	Percent
Male	57	34,8
Paisa last names	122	74,4
Diagnosis		
BD I	155	94,5
BD II	9	5,5
Predominant polarity		
Maniac	108	65,9
Depressive	24	14,6
Indeterminate	32	19,5
Comorbidity		
Alcohol	12	7,3
Other substances	15	9,1
Other mental disorders	26	15,9
Prior episodes of psychosis	122	74,4
Prior suicides attempts	54	32,9
Ancestry		
European	52	31,7
Amerindian	90	54,9
African	4	2,4
Indeterminate	18	11
Response to lithium*		
NR	45	27,4
PR	92	56,1
GR	27	16,5

	Median	IQR
Age	46	35 - 53
BD age of onset	19	15 - 28
Number of affective episodes		
Maniacs	6,3	2 - 7
Depressives	1	1 - 3,5
Totals	9,69	4 - 10,8
ALDA TS	3	1 - 5,5

Abbreviations: RIC: Interquartile Range, TS. Total Scale. NR: No response, PR: partial response, GR: Good response

*Response to lithium. According to ALDA´s TS scale. NR (TS<2), PR: (TS2-6), GR: (TS>=7)

Table 2.

Model fit indices for LCA in a sample of subjects with Bipolar Disorder (n=164)

Number of classes	BIC	LL
One	10937,89	-4510,17
Two	10132,08	-4030,77
Three	9924,09	-3850,27
Four	9887,85	-3755,65
Fice	9854,72	-3662,59
Six	9824,44	-3570,96
Seven	9840,61	-3502,54
Eight	9850,04	-3434,75
Nine	9960,89	-3409,69
Ten	9917,49	-3311,49

Abbreviations: LL: *Log-Likelihood;* BIC: *Bayesian Information Criterion*

Table 3.

Clinical, sociodemographic and ancestry variables of six empirical subtypes acquired from latent class analysis in the “paisa” genetic isolate. (n=164)

VARIABLES	SUBTYPE 1 (n=39)	SUBTYPE 2 (n=30)	SUBTYPE 3 (n=30)	SUBTYPE 4 (n=31)	SUBTYPE 5 (n=20)	SUBTYPE 6 (n=14)
Percentage of the sample	23,7	18,2	18,2	18,9	12,2	8,5
Male gender, n (%)	12 (27,0)	11, (36,7)	6 (20,0)	11(36,7)	11 (55,0)	5 (35,7)
Paisa last name, n (%)	32 (82.05)	90 (66.7)	90 (66.7)	24 (77,4)	14 (70)	12 (85.7)
Diagnosis, n (%)						
BD I	37 (94,9)	30 (100,0)	29 (96,7)	28 (93,3)	17 (85,0)	14 (100,0)
BD II	2 (5,1)	0 (0,0)	1 (3,3)	2 (6,7)	3 (15,0)	0,00 (0,0)
Predominant Polarity						
Indeterminate	5 (12,8)	2 (6,7)	10 (33,0)	5 (16,7)	8 (40,0)	2 (14,3)
Depressive	6 (15,4)	2 (6,7)	3 (10,0)	4 (13,3)	6 (30,0)	3 (21,4)
Manic	28 (71,8)	26 (86,7)	17 (56,7)	21 (70,0)	6 (30,0)	9 (64,3)
Prior Psychosis, n (%)	29 (74,4)	26 (86,7)	21 (70)	23 (76,7)	14 (70)	9 (64,3)
Prior suicide attempts, n (%)	12 (30,8)	10 (33,3)	10 (33,3)	7 (23,3)	9 (45)	6 (42,9)
Substance use disorder n (%)	4 (10,3)	3 (10,0)	1 (3,3)	1 (3,3)	2 (10,0)	1 (7,4)
Other mental disorder, n (%)	11 (28,2)	4 (13,3)	5 (16,7)	2 (6,7)	3 (15,0)	1 (7,4)
Age, Me (IQR)	43 (33 – 54)	44 (37 – 52)	42 (35 – 49)	49 (43 – 55)	47 (39 – 53)	47 (32 – 53)
BD age of onset, Me (IQR)	23 (18 - 31)	18 (17 – 26)	17 (14 – 28)	22 (18 – 29)	17 (14 - 21)	15 (14 – 18)
Affective episodes, Me (IQR)						
Total	5 (3 – 6)	4 (3 – 4)	9 (7 – 10)	6 (5 – 9)	25 (21 – 30)	13 (10 – 25)
Manic	3 (2 – 4)	3 (2 - 3)	6 (5 - 7)	5 (2 - 7)	17 (5 – 26)	9 (7 - 12)
Depressive	1 (0 – 2)	1 (0 - 1)	3 (1 - 4)	1 (0 – 3)	12 (2 – 12)	5 (2 – 9)
Hospitalization	3 (1 – 4)	2 (1 – 3)	5 (2 – 8)	4 (1 – 6)	9 (1 – 19)	6 (2 – 12)
Response to lithium, n (%)						
NR	9 (23,1)	6 (20,0)	12 (40,0)	6 (20,0)	10 (50,0)	2 (14,3)
PR	20 (51,3)	20 (66,7)	17 (56,7)	18 (60,0)	9 (45,0)	7 (50,0)
GR	10 (25,6)	4 (13,3)	1 (3,3)	20 (20,0)	1 (5,0)	5 (35,7)
ALDA TS	4 (2 – 7)	3 (2 – 5)	2 (0 – 4)	5 (2 – 6)	1,5 (1 – 4)	5 (3 – 7)
Ancestry, Me (IQR)						
European	0,65 (0,58-0,75)	0,13 (0,07-0,21)	0,26 (0,11-0,48)	0,06 (0,03 -0,10)	0,15 (0,05-0,34)	0,66 (0,60-0,78)
Amerindian	0,19 (0,08-0,28)	0,76 (0,67-0,80)	0,41 (0,24-0,59)	0,90 (0,85-0,94)	0,74 (0,53-0,84)	0,10 (0,05 -0,15)
Afro-American	0,12 (0,03-0,23)	0,11 (0,04-0,15)	0,30 (0,16-0,45)	0,02 (0,01-0,04)	0,04 (0,02-0,14)	0,24 (0,07-0,27)

Abbreviations: Me: median; IQR interquartile range, TS. Total Scale. NR: No response, PR: partial response, GR: Good response

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